Remarks

Claims 1-42 are pending in the application. Claims 16-42 have been withdrawn. As requested, Applicant reaffirms the election of Group 1, claims 1-15, in a response to Restriction Requirement that was mailed on September 14, 2005. Claims 1-15 stand rejected.

Rejection of claims 1-15 on the ground of nonstatutory obviousness double patenting

The Examiner has rejected claims 1-15 on the ground of nonstatutory double patenting as being unpatentable over claims 3 and 4 of U.S. Patent No. 6,551,993 to Schneider (hereinafter "Schneider"). Specifically, the Examiner alleges that although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims are directed to methods of treating Parkinson's disease comprising administering levodopa/carbidopa and a partial glycine agonist selected from the group consisting of D-cycloserine, D-serine and serine racemase. The Examiner states further that the "high dose" required in claim 1 of the present application is disclosed in column 6 of Schneider. Applicant respectfully traverses this rejection for the following reasons.

The MPEP §804 states, in relevant part:

> A double patenting rejection of the obviousness-type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

The MPEP §2142 also states in relevant part the following:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach

> or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Claim 1 of the present application recites a method for treating Parkinson's disease in a subject comprising administering levodopa and a high dose of a partial glycine agonist to the subject in order to increase the efficacy of levodopa or decrease the frequency and severity of levodopa induced side effects. Claims 3 and 4 of Schneider recite a method of treating cognitive and motor dysfunction in mammals having Parkinson's disease comprising administering a therapeutically effective amount of a partial glycine agonist, wherein the partial glycine agonist is D-cycloserine, D-serine or serine racemase. Based upon the Schneider specification, a therapeutically effective amount of partial glycine agonist for treating cognitive and motor dysfunction is a low dose, not a high dose, as recited in the instant claims. Further, Schneider claims 3 and 4 do not specify treating Parkinson's disease wherein the efficacy of administered levodopa is enhanced, or the frequency and severity of levodopa-induced side effects is reduced.

The first prong of the *In re Vaeck* test, the requirement that the references themselves or the knowledge in the art must provide some suggestion or motivation, has not been met by Schneider. In this instance, there is no incentive or motivation to modify the claimed invention of Schneider to arrive at the present invention. Schneider claims 3 and 4 do not examine the effect of high doses of a partial glycine agonist in enhancing the efficacy of levodopa or in reducing the frequency and severity of levodopa-induced side effects, such as dyskinesia or dystonia. In addition, Schneider discloses that high doses of a partial glycine agonist are <u>not</u> useful in treating the cognitive defects associated with Parkinson's disease (See column 4, lines 31-35) thereby teaching away from their usefulness in treating Parkinson's disease and negating the requisite motivation required to render the instant invention obvious.

The second prong of the *In re Vaeck* test, the requirement that there be a reasonable expectation of success, is similarly not met in this instance. The Examiner asserts that Schneider discloses that by combining a partial glycine agonist with existing anti-Parkinsonian treatments, motor and cognitive function can be enhanced. However, claims 3

and 4 of Schneider specifically recite the use of a "therapeutically effective amount" of a partial glycine agonist which is defined in the Schneider specification as a low dose. As such, it can not be inferred from the Schneider claims that combining levodopa with a high dose of partial glycine agonist would enhance the efficacy of the levodopa or reduces the frequency and severity of levodopa-induced side effects (i.e., dyskinesia) as claimed in the present application.

In addition to the requirements set forth above, in order to establish a *prima facie* case of obviousness, the prior art reference(s) in combination must teach or suggest all of the claim limitations. Schneider fails to teach or suggest all of the claim limitations. Neither the Schneider claims nor the supporting disclosure in the Schneider specification suggest that treatment with levodopa and a high dose of a partial glycine agonist will enhance the efficacy of levodopa or reduce the frequency and severity of levodopa-induced side effects. Thus, Schneider does not meet the third prong of the *In re Vaeck* test.

A person of ordinary skill in the art would not conclude that the invention defined in the instant claims is an obvious variant of Schneider claims 3 or 4. The test to establish a *prima facie* case of obviousness (in this case, obviousness-type double patenting) has not been met. Reconsideration and withdrawal of the rejection for obviousness-type double patenting is respectfully requested.

Rejection of claims 1-15 under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 1-15 under 35 U.S.C. §112, second paragraph, for allegedly being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner alleges that Applicant does not provide a limiting definition of the term "high dose" of claim 1. Applicant respectfully traverses this rejection for the following reasons.

It is settled law that the Applicant is entitled to have the claims construed in connection with the other parts of the application. *See Autogiro Co. v. U.S.*, 155 USPQ 697 (Ct. Cls. 1967). Therefore, the claims must be interpreted in light of the other parts of the application including the disclosure in the specification and the definitions provided therein. Applicants respectfully submit that the specification makes clear the limits of the term "high

dose." Specifically, the specification teaches that a high dose is one which produces a partial glycine agonist concentration at which the partial glycine agonist antagonizes the glycine binding site of the NMDA receptor in the brain of a subject (See specification page 6, lines 7-9). The specification also teaches that the concentration of partial glycine agonist is preferably greater than 1 mg/kg and most preferably between 8 mg/kg and 12 mg/kg (See specification page 6, lines 10-14). Therefore, one skilled in the art would have understood the term "high dose" based upon the disclosure provided in the specification.

Further, the Examiner states in her nonstatutory obviousness-type double patenting rejection that the "high dose" required by instant claim 1 is met by the dosing disclosure in Schneider (US Patent No. 6,551,993) in columns 6-7. If the term "high dose" is sufficiently clear that the Examiner can conclude that the feature is allegedly disclosed in a reference, then it cannot be indefinite. Thus, the term "high dose" must be recognizable to one of ordinary skill in the art for the Examiner to conclude, albeit erroneously, that the feature is allegedly met by the prior art. As such, there is nothing vague or indefinite about claims 1-15 under 35 U.S.C. §112, second paragraph. Reconsideration and withdrawal of the §112 rejection is respectfully requested.

Rejection of claims 1-15 under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 1-15 under 35 U.S.C. §112, first paragraph, as lacking a clear written description of the invention and of the manner and process of practicing it, and in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to practice the same, and, as not setting forth the best mode contemplated by the inventor to carry out the invention. The Examiner notes that specification shows that D-cycloserine is administered with levodopa, but alleges that there is no guidance provided for the administration of any other partial glycine agonist such as D-serine, ACPC and serine racemase. The Examiner states that there is no showing that the Applicant had possession of the claimed invention of therapeutic treatments involving any partial glycine agonist other than D-cycloserine.

At this time, Applicant is confused by the Examiner's rejection. By quoting the entirety of 35 U.S.C. §112, first paragraph in the rejection (including the requirement of a

best mode), it is unclear as to which part of Section 112, first paragraph, the rejection pertains (i.e., written description, enablement or best mode). Applicant believes that the Examiner is attempting to make a rejection based upon written description, and will respond accordingly.

With regard to the written description requirement, "[t]he primary concern is factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 116 (Fed. Cir. 1991).

The partial glycine agonists are a well-defined category of agents. Representative partial glycine agonists are identified in the specification: D-cycloserine, D-serine, ACPC and serine racemase (page 6, lines 1-6). Details are provided regarding the conditions of their use according to the invention, such as route of administration (page 6, lines 27-page 7, line 13), dosage (page 7, lines 14-19), formulation (page 10, line 28 - page 13, line 6), and treatment regimes and patient monitoring (page 7, lines 4-13; page 7, line 20 – page 9, line 29)). The specification contains experimental results with respect to the successful use of a representative partial glycine agonist, D-cycloserine. The specification reasonably imparts to those skilled in the art that applicant had possession of the claimed invention

The Examiner states that the present level of skill in the neurology art in effective treatment modalities for Parkinson's is immature. Thus, the Examiner alleges that it would have been reasonable to require a more detailed written description directed to treatment involving the administration of the partial glycine agonists D-serine, ACPC and serine racemase. The details are appropriate for all partial glycine agonists. Moreover, it must be appreciated that Applicant is not claiming a novel treatment for Parkinson's disease. Rather, Applicant is claiming an *improvement* over a well-known preexisting treatment for Parkinson's disease, which treatment utilizes the drug. Levodopa was approved for treatment of Parkinson's Disease in 1970. Examiner will no doubt recognize that levodopa therapy is still the present "gold standard" for treating Parkinson's Disease. In the method of the present invention, a partial glycine agonist is administered not as a *de novo* therapeutic agent, but merely to enhance the efficacy of the well-known primary agent, levodopa, or to reduce the frequency or severity of levodopa's side effects. Applicants'

invention should not be judged as if it were a *de novo* treatment modality for Parkinson's Disease.

Further, the Examiner provides no evidence to support her assertion that the present level of skill in the neurological arts relevant to modalities for treating Parkinson's Disease is "immature". The MPEP §2163.04 states in relevant part:

> The inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97. [Emphasis added]

The initial burden of proof in making a written description rejection lies with the Examiner and, in this instance, that burden has not been met. Merely stating that the level of skill for treating Parkinson's disease is immature does not provide a reasonable basis for challenging the adequacy of the description of the invention, and does not satisfy the Examiner's initial burden of presenting evidence to satisfy the requisite preponderance of the evidence standard for maintaining the Section 112 rejection. In any event, Applicant disputes that treatment of Parkinson's with levodopa, the only segment of Parkinson's' therapeutics that is relevant here, is in any way "immature". Levodopa was the first drug approved specifically for Parkinson's Disease, and remains the drug of choice for that disorder today.

Submitted herewith is Declaration by the inventor, Jay S. Schneider, pursuant to 37 C.F.R. §1.132, demonstrating that the treatment of a Parkinsonian monkey with ACPC decreased the severity and frequency of levodopa induced dyskinesia by approximately 30%. ACPC is one of the representative partial glycine agonists identified in the specification. The experiment serves to verify the teachings of the specification as to the utility of partial glycine agonists for decreasing the severity and frequency of levodopa

induced dyskinesia. The experiments were performed using similar procedures as those described in the specification (See Examples, beginning on page 13, line 10).

Applicant requests reconsideration and withdrawal of the Examiner's rejection under 35 U.S.C. §112, first paragraph.

Rejection of claims 1-15 under 35 U.S.C. §103(a)

The Examiner has rejected claims 1-15 as being allegedly obvious over U.S. Patent No. 5,668,117 to Shapiro (hereinafter "Shapiro") in view of Schneider. Specifically, the Examiner alleges that Shapiro teaches a pharmaceutical composition for use in the treatment of Parkinson's disease optionally comprising levodopa or levodopa combined with the peripheral dopa decarboxylase inhibitor carbidopa and the partial glycine agonist D-cycloserine. Examiner acknowledges that Shapiro fails to characterize the dosage of D-cycloserine as "high", but alleges that this deficiency is remedied by Schneider. Examiner alleges that Schneider teaches a dosage described as "large" in column 7, lines 2-3, and that this 8 mg/kg dosage meets the requirement of "high dose" of claim 8 of the present application.

Claim 1 of the present application recites a method for treating Parkinson's disease in a subject comprising administering levodopa and a high dose of a partial glycine agonist to the subject, wherein the severity of the levodopa side effects, for example dyskinesia and dystonia, is reduced. Shapiro teaches neither the use of high doses of a partial glycine agonist to treat Parkinson's disease nor the treatment of Parkinson's disease by affecting the efficacy of levodopa or reducing the frequency and severity of its side effects.

At the outset, it must be noted that Schneider U.S. Pat. 6,551,993 (mistakenly referenced as "5,668,117" in the office action) cannot be used to correct the deficiencies in Shapiro. The inventorship of the Schneider patent is identical to the inventorship of the present application. An inventor's own work is not prior art absent a statutory bar under 35 USC 102 (b), which requires the invention to be "patented or described in a printed publication ... more than one year prior to the date of application for patent". The Schneider patent issued on April 22, 2003, which is not more than one year before the filing date of the present application. Therefore, Applicant's prior US patent, which issued within the year

before the present application's filing date, cannot be used against him as prior art. However, of record is the published international application, WO 01/12190, corresponding to Pat. 6,551,993. WO 01/12190 published on Feb. 22, 2001. Hence, Applicant will address the substance of the instant combination rejection.

The first prong of the *In re Vaeck* test, the requirement that the references themselves or the knowledge in the art must provide some suggestion or motivation to arrive at the present invention, has not been met in this instance. There is no incentive or motivation to modify the teachings of Shapiro to arrive at the present invention. Shapiro does not disclose the use of a partial glycine agonist, specifically high doses of a partial glycine agonist, in combination with levodopa to enhance the efficacy of levodopa or to reduce the frequency and severity of levodopa-induced side effects. In fact, Shapiro does not even mention any levodopa-induced side effects (i.e., dyskinesia or dystonia). Shapiro merely discloses the potential use of D-cycloserine in combination with a long list of other compounds and states that the disclosed experimental therapeutic approaches for clinical treatment of Parkinson's disease may or may not be used in conjunction with levodopa (See Shapiro column 2, lines 24-27). As such, Shapiro does not suggest or motivate one of ordinary skill in the art to treat Parkinson's disease with a high dose of a partial glycine agonist in combination with levodopa in order enhance the efficacy of the levodopa or to reduce the frequency or severity of levodopa-induced side effects.

Schneider cannot correct the defects of Shapiro as Schneider only discloses treating Parkinson's disease by stimulating the NMDA receptor with a low dose of partial glycine agonist. Schneider explains that a low dose of partial glycine agonist is used because it has an agonistic effect on the NMDA receptor as opposed to the antagonistic effect that a high dose of partial glycine agonist has on the NMDA receptor. Thus, there is a clear difference in outcome when utilizing a high dose of partial glycine agonist as does the present invention compared to utilizing a low dose of partial glycine agonist as does Schneider to treat Parkinson's disease. Further, Schneider tested a high dose of partial glycine agonist (D-cycloserine) in treating the cognitive defects associated with Parkinson's disease but demonstrated it to be ineffective for such use (See Fig. 2) thereby not motivating one of ordinary skill in the art to utilize the same treatment to remedy other defects associated with

the disease. Therefore, Shapiro, when examined in view of Schneider, does not provide the requisite suggestion or motivation to reach the present invention. In fact, Schneider teaches away from administration of a high dose of partial glycine agonist.

The second prong of the *In re Vaeck* test, the requirement that there be a reasonable expectation of success, is similarly not met in this instance. There is nothing in the disclosure of Shapiro that would suggest any expectation of success in utilizing high doses of a partial glycine agonist in combination with levodopa to reduce levodopa-induced side effects or to enhance the efficacy of levodopa itself. Shapiro neither discloses reducing the frequency and severity of a side effect induced by levodopa treatment nor does it disclose enhancing the efficacy of levodopa with a high dose of a partial glycine agonist. Shapiro merely contains an extensive list of compounds that may or may not be used in combination with one another. As such, it does not provide the guidance that a skilled artisan would need to expect success in practicing the present invention but rather supplies the skilled artisan with an "invitation to experiment" by trying a multitude of random combinations of compounds to treat Parkinson's disease. That is, Shapiro does no more than propose a desirable concept, while providing no basis upon which to actually develop and practice such a concept.

Thus, the Examiner has done no more than identify an "obvious-to-try" situation. An invention is "obvious-to-try" where the prior art provides either no indication of the critical parameters or no direction as to which of many possible choices is likely to be successful. *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 874 F.2d 804, 807 10 USPQ2d 1673, 1681 (Fed.Cir. 1988). In an "obvious-to-try" situation, the general disclosure may pique a scientist's curiosity, but fail to indicate how to obtain a desired result. *In re Eli Lilly & Co.*, 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed.Cir. 1990). Similarly, Shapiro mentions that levodopa and D-cycloserine may be combined; however, it fails to teach that a combination of levodopa and a high dose of partial glycine agonist would result in enhancing the efficacy of the levodopa or reduce the frequency and severity of levodopa-induced side effects.

Shapiro also offers no reasonable expectation of success when examined in view of Schneider as Schneider only discloses the use of low doses of partial glycine agonist to treat

Parkinson's disease. Schneider does not disclose the use of high doses of partial glycine agonist in combination with levodopa to decrease the frequency or severity of a levodopa-induced side effect or to enhance the efficacy of levodopa. Indeed, Schneider teaches away from the present invention by demonstrating the ineffectiveness of high doses of partial glycine agonists in treating the cognitive defects associated with Parkinson's disease. As such, one of ordinary skill in the art would not predict success in using a high dose of partial glycine agonist to reduce the frequency and severity of levodopa-induced side effects, such as dyskinesia and dystonia, or to enhance the efficacy of levodopa. Therefore, Shapiro, when combined with Schneider, does not provide the skilled artisan with a reasonable expectation of success in practicing the present invention.

In addition to the requirements set forth above, in order to establish a *prima facie* case of obviousness, the prior art reference(s) must teach or suggest all of the claim limitations. Similar to the other prongs of the *In re Vaeck* test, Shapiro and Schneider fail to teach or suggest all of the claim limitations as neither reference teaches the treatment a levodopa-induced side effect or enhancing the efficacy of levodopa by administration of a high dose of a partial glycine agonist in combination with levodopa. As such, the three prong test to establish a *prima facie* case of obviousness has not been met so reconsideration and withdrawal of the Section 103(a) rejection is respectfully requested.

The claims remaining under examination in the application are believed in condition for allowance. An early action toward that end is earnestly solicited.

Respectfully submitted

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